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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,439	02/25/2002	Patrice Andre	111737	6420

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EXAMINER
CHEN BROWN, STACY

ART UNIT	PAPER NUMBER
1648	11

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,439	ANDRE ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-24* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-22 and 24* is/are rejected.

7)☒ Claim(s) *1-3,6-8 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I, claims 1-15 and 17-18 with traverse is acknowledged. Claims 1-15 and 17-24 are pending. Claim 23 is withdrawn from consideration being drawn to a non-elected invention. Applicant mainly argues that the special technical feature of Group I is shared with Groups II, III and V. Therefore, claims 1-15, 17-22 and 24 are examined on the merits.

Information Disclosure Statement

2. The following references cited in the Information Disclosure Statement lack dates:

- Dixon *et al.*, *J. Biol. Chem.*, 266 :5080-5086.
- Roda *et al.*, *J. Steroid Biochem.*, 13:449-454.

Applicant is requested to supply the missing dates in order for the references to be properly cited.

Claim Objections

3. Claims 1, 2, 3, 6, 7, 8 and 21 are objected to because of the following informalities:

- Claim 1, the acronym "LVP" should be spelled out at its first recitation.
- Claim 2, "associative with human immunoglobulins" should be "associated with human immunoglobulins".
- Claim 3, the acronyms "LSR" and "LDL" should be spelled out at their first recitation.
- Claim 3, "surface receptor from" should be "surface receptor for".
- Claim 6, "dendritic" is misspelled.

- Claim 7, "permissives" should be "permissive".
- Claim 8, "derivative of fatty acid" should be "derivative of the fatty acid".
- Claim 21, the structure of the sentence is confusing. Suggested language is "A diagnostic kit comprising the diagnostic composition of claim 20."

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 17-22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of culturing HCV viruses using lipo-viro-particles (LVPs), does not reasonably provide enablement for culturing all viruses from the Togaviridae or Flaviviridae families using LVPs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The nature of the invention is the culturing of viruses from the Togaviridae or Flaviviridae families by infecting cells with LVPs derived from the serum or plasma of infected subjects. The breadth of the claims is unreasonable, encompassing the use of LVPs from any virus within the Togaviridae or Flaviviridae families. However, the specification has only shown that LVPs from HCV-infected samples have been isolated (specification, page 6, lines 13-31). The state of the art shows the existence of particles associated with lipoproteins (Thomsen *et al.*, 1993, *Med. Microbiol. Immunol.* 182:639), which Applicant's have named LVPs. The level of

predictability in the art is not high with regard to finding LVPs in other viruses, since only HCV has been shown. The amount of direction provided by the inventor and the working examples are limited to HCV-infected samples. Given the state of the art, the amount of guidance in the specification, the working example and the low predictability, it would require undue experimentation to make or use LVPs from any virus of the Togaviridae or Flaviviridae families, except HCV, since LVPs have only been found in HCV-infected samples.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, 17-22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claims 1, 4, 6 and 9 should recite proper Markush language, "selected from the groups consisting of...and...".
- Claims 5, 9, 12 and 13, "preferably", "in particular", "advantageously" and "such as" render the claims indefinite because it is unclear whether the limitations following the phrases are part of the claimed invention. See MPEP § 2173.05(d).
- Claims 1, 17, 19 and 24 are missing method steps to complete the method preamble.
    - Claim 1 is drawn to a method for culturing, propagating and replicating viruses, however there are no culturing steps beyond contacting the LVP fraction with cells.

- The method steps in claim 17 skip from contacting the LVP fraction with cells, to purification of particles. There are no steps in between indicating propagation or replication and harvest.
- Claim 19 is drawn to a method of obtaining antibodies or antibody fragments, however the only method step is immunizing an animal with viral particles. There are no steps indicating the binding of antibodies to the viral particles and subsequent steps of separating out the antibodies/viral particles from the animal.
- Claim 24 is drawn to a method of screening and/or selecting an antiviral molecule, however the method steps fail to indicate how an antiviral molecule is detected and subsequently qualified and selected as a an antiviral molecule.

- Claim 4 lacks antecedent basis for "lipoproteins" in independent claim 1.
- Claims 17-19 and 22 lack antecedent basis for "viral particles" and "polypeptides" in independent claim 1. Claim 1 recites that viruses are obtained; there is no mention of viral particles or polypeptides.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15, 17-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houghton *et al.* (5,679,342) in view of Yoshikura *et al.* (5,766,919), Monazahian *et al.* (*J. Med. Virol.*, 1999, 57:223-2239), Agnello *et al.* (*PNAS*, 1999, 96 :12766-12771) and Bucci *et al.* (*Atherosclerosis*, 1998, 137:329-340).

The claims are drawn to a method for culturing, propagating and replicating, *in vitro*, viruses from the Togaviridae or Flaviviridae families. The method steps comprise obtaining an LVP fraction from serum or plasma of a virus-infected patient, contacting the LVP fraction with permissive cells in a medium containing an unsaturated fatty acid, in particular, oleic acid. The receptor for the lipoproteins is the LSR or the surface receptor for LDLs. The permissive cells can be human hepatocarcinoma cells of the PLC/PRF/5 cell line. The medium can also contain an apoptosis-modulating agent such as interferon. The culture medium is supplemented with glutamine, penicillin, streptomycin and calf serum. The infected cells are subcultured and the presence of virus is determined by RT-PCR. The infected cells can be used in a method to screen antiviral molecules. The virus obtained from the culturing method is purified, and the resulting virus is used to detect antibodies. Also claimed are a diagnostic composition, kit and immunization comprising the virus obtained from the culturing method.

Houghton teaches a method of HCV infection, comprising contacting an infective HCV source with hepatocyte cells, such as PLC/PRF/5 (abstract and col. 13, line 43). Stimulatory protein factors can be present such as interleukin (col. 12, lines 36-45). Houghton uses the resulting HCV antigens to detect antibodies, screen putative antiviral agents (col. 19, lines 28-39 and col. 20, lines 29-55). The viruses can be used for diagnostics and immunogenic compositions with adjuvants, pharmaceutical carriers and excipients (col. 14, lines 20-29 and col.

18, lines 33-58). Houghton fails to disclose the steps of 1) obtaining the LVP fraction from serum or plasma of an infected patient, and 2) administering a saturated fatty acid.

However, Yoshikura obtains HCV from infected chimpanzees' serum and infects a T cell line (example 2). Yoshikura found that HCV having lower infectivity were bound to an anti-HCV antibody and forms an immunocomplex when contacted with an anti-human immunoglobulin antibody (abstract).

Monazahian and Agnello teach that the LDL receptor is a receptor for HCV (abstracts). They discovered that the addition of LDL to cells expressing the LDL receptor were not bound by HCV (abstracts).

Bucci teaches that oleic acid facilitates the binding of LDL to cells expresses an LDL receptor. Bucci used BHK-21 cells, which "possess a classical LDL receptor" (abstract).

It would have been obvious to obtain the LVP fraction from an infected subject's serum to infect the cells of Houghton. Considering that the LVP fraction is inherently present in the supernatant of centrifuged serum and plasma, and the method of Yoshikura obtains HCV derived from the supernatant of plasma, one would have expected the LVP fraction to be present. Since Yoshikura's method is similar to Houghton, with regard to deriving virus from plasma, one would have been motivated to culture the virus in the hepatocyte cells because Houghton discloses that candidate cell systems for HCV-infection are hepatocyte cell systems, among others (col. 11, lines 29-40). One would have had a reasonable expectation of success that the fraction of Yoshikura would have grown in the cells of Houghton because the two methods used to obtain the virus fraction are functional equivalents.

It would have been obvious to use oleic acid in Houghton's method because Monazahian and Agnello teach that the LDL receptor is responsible for HCV infection, and Bucci teaches that oleic acid facilitates the binding of the LDL receptor ligand to the receptor. One would have been motivated to use oleic acid in order to facilitate the binding of HCV to the LDL receptor because Houghton's method is to promote HCV infection and distinguish between different levels of infectivity (abstract). One would have had a reasonable expectation of success that the LDL receptor of Houghton's permissive cells would have been receptive to HCV because Bucci used a cell that has a standard LDL receptor.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time of the invention. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

7. No claim is allowed.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 located in Crystal Mall 1. The Fax number

for Art Unit 1648 is (703) 308-4426. All Group 1600 Fax machines will be available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stacy B. Chen, whose telephone number is (703) 308-2361. The Examiner can normally be reached on Monday through Friday from 7:30 AM-4:00 PM, (EST). If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, James C. Housel, can be reached at (703) 308-4027. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SBC

Stacy B. Chen
August 8, 2003

James C. Housel 8/8/03
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